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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,046	12/10/2003	Scott M. Walsh	BSYNEXUS-10148	8450

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/733,046	WALSH ET AL.	
	Examiner	Art Unit	
	VANESSA L. FORD	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-46 and 55-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-46 and 55-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed August 4, 2008. Claims 33 and 36 have been amended. Claims 1-32 and 47-54 have been cancelled. Claims 33-46 and 55-75 are under examination.

Applicant's Declaration filed under 37 C.F.R. 1.132 by Dr. James J. Mond was filed October 10, 2007 is acknowledged. However, this declaration is insufficient to overcome any art rejections of record.

Objection/Rejection Withdrawn

2. In view of Applicant's amendment and remarks the following rejections are withdrawn.

a) objection of claim 2, pages 23, paragraph 8.

b) rejection of claim 36 under 35 U.S.C. 112, second paragraph, page 24, paragraph 9.

Rejections Maintained

3. The rejection under 35 U.S.C. 102(b) paragraph is maintained for claims 33-37, 39-40, 42-46, 56-61 and 63-75 for the reasons set forth on pages 3-6, paragraph 3 of the previous Office Action.

The rejection is reiterated below:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection was on the grounds that Blackburn et al (U.S. Patent 5,762,948) teach a method of disinfecting (decolonizing) bacterial populations comprising topically applying to a patient a topical composition comprising nisin and lysostaphin (the Abstract, column 3 and columns 11 –12, Example 7). Blackburn et al teach that the lantibiotics are present at 25 ug/ml to 500 ug ml in the compositions of the invention (column 15, claim 5). Therefore the prior art teaches a topical composition comprising an antibiotic from about 0.1 to about 10.0 wt %. Blackburn et al teach the compositions of the invention comprise chelating agents such as EDTA (column 3), a carrier for topical application such as a wipe or liquid (see the Abstract, column 3 and column 5), anti-infective active agents such as such as chlorhexidine (column 3), a skin absorption promoter such as monoglycerides and fatty acids (column 4) and surfactants such as polysorbate 20 (column 4). Blackburn et al teach that composition can comprise emulsifers (column 4). Blackburn et al teach a reduction in Staphylococcus aureus (columns 12-14). Claim limitations such as "wherein the concentration of lysostaphin in said composition is lower than the minimum inhibitory concentration of lysostaphin when used independently", "wherein the concentration of lantibiotic in said composition is lower than the minimum inhibitory concentration of lantibiotic when used independently", wherein the concentration of lysostaphin and lantibiotic in said composition is lower than the minimum inhibitory concentration of lysostaphin and lantibiotic when used independently" would be inherent in the teaching of the prior art.

Applicant Arguments

A) Applicant urges that a claim is anticipatory only if each and every element of the claims is found expressly on inherently within a single prior art reference. Applicant urges that the Examiner has acknowledged that lysostaphin is not a lantibiotic. Applicant urges that Blackburn et al do not teach or describe a lysostaphin. Thus, Blackburn et al do not each and every element of the claimed invention. Applicant urges that Blackburn et al fail to describe the details of decolonizing bacterial populations comprising topically applying to a patient a topical composition comprising lysostaphin and a lantibiotic.

B) Applicant urges that the Declaration submitted by Dr. James J. Mond filed under 37 C.F.R. 1.132 urges that there is no way to know how two complex compounds lysostaphin and nisin would interact when combined. And whether they would be functional to treat a would or skin infection. Applicant urges that Blackburn et al do not teach compositions used in the claimed method comprise 0.1 wt% lantibiotics and 0.1 wt% nisin.

C) Applicant urges that Blackburn et al do not place the public in possession of the claimed invention.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed August 4, 2008 have been fully considered but they are not persuasive.

A) The claims are directed to a method of decolonizing bacterial populations comprising a lysostaphin and one or more lanibiotics. Blackburn et al teach a composition comprising nisin, subtilin, epidermin, gallidermin, cinnamycin, duramycin, ancovenia or Pep5 (all of which are lantibiotics). Blackburn et al also teach that lysostaphin may also be employed with the lantibiotic composition. See column 3. Thus, The Examiner disagrees with Applicant assertion that Blackburn et al do not teach or suggest the claimed invention.

To address Applicant's comment's regarding Blackburn et al not teaching a method of decolonizing bacterial populations. Blackburn et al teach a method of disinfecting (decolonizing) cow teat skin (see the Abstract). Blackburn et al teach that a method of decolonizing bacterial populations comprising topically applying to a patient in need thereof at a bacterially infected site in Example 11. Example 11 of Blackburn et al teach that cows infected with *Staphylococcus aureus* and *Staphylococcus agalactiae* and wipes of the invention were employed at the cow teat (bacterially infected site) to reduce the incidence of mastitis. Therefore, Blackburn et al teach a method of decolonizing bacterial populations.

B) To address the Declaration submitted by Dr. James J. Mond filed under 37 C.F.R. 1.132, the declaration is insufficient to overcome the rejection under 35 U.S.C. 102(b).

To address the comments raised in the declaration regarding the ability of lysostaphin and lantibiotics to interact, it is known in the art that lysostaphin as well as lantibiotics have bactericidial activity. Thus, both are effective at eradicating bacterial infection. See columns 1 and 4 of Blackburn et al. It should also be noted that 2144.06 states that:

> It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted)".

To address the comments raised in the declaration regarding the concentrations used in compositions, Blackburn et al teach that these bactericidal agents (lantibiotics an/or lysostaphin) may be used in concentration of 25 ug/ml to 500 ug/ml. See column 15, claim 5 of Blackburn et al. Regarding the specific concentrations listed in the instant claims, MPEP 2144.05 states, “Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*,

874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)."

C) To address Applicant's comments regarding possession, it should be not that this a rejection made under 35 U.S.C. 102 and not 35 U.S.C. 112 first paragraph. However, Blackburn et al adequately describe the invention in Example 11, as outlined above.

In view of all of the above this rejection is maintained.

4. The rejection of claims 33-37, 39-40, 42-46, 55-61 and 63-75 under 35 U.S.C. 103(a) is maintained for the reasons set forth on pages 6-13, paragraph 4 of the previous Office Action.

The rejection is reiterated below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection was on the grounds that the claims are drawn to a method of decolonizing populations comprising topically applying to a patient in need thereof at a bacterially infected site a topical composition comprising lysostaphin and one or more lantibiotics.

Daley et al (U.S. Patent 5,342,612) teach a method of eliminating bacterial (*Staphylococcus)* infections in bovine mammary glands comprising administering a composition comprising bacteriostatic peptide such as lysostaphin or nisin (column 4

and columns 11-13). Daley et al teach that the compositions of the invention contain 0.01% to about 50% by weight of the bacteriostatic peptide in the total composition (column 4). Daley et al do not teach using other lantibiotics in the method of the invention.

Blackburn et al (U.S. 4980,163) teach compositions comprising bactericides (see the Abstract). Blackburn et al teach compositions comprising lysostaphin, nisin a chelating agent such as EDTA and a surfactant (the Abstract and columns 3-4). Blackburn et al teach that compositions may include antibiotics, copolymers and surfactants which include emulsifers and fatty acids (column 4). Blackburn et al teach that suitable carrier for the bactericides include organic solvents, buffers and polymers (column 4). Blackburn et al teach that compositions of the invention have enhanced broad range bactericide activity against bacteria such as *S. aureus* and *P. aeruginosa* (claims 18 and 19). Blackburn et al teach that the concentration of lysostaphin is about 0.1 to 100 μg/ml and the concentration of nisin is between about 0.1 to 300 μg/ml (column 4) (see claims 20-21). Blackburn et al teach the compositions comprising lysostaphin and nisin provide broad range bactericidal activity against bacterial infections (see the Abstract and columns 6-7). Blackburn et al teach that bactericidal activity and the overall speed of bactericidal activity is enhanced when two bacteriocins are combined in one composition (column 2).

Claim limitations regarding how many times the composition is applied to the infected site would be a matter of optimizing experimental parameters (see instant claims 68-71).

It would be *prima facie* obvious at the time the invention was made to modify he method of eliminating bacterial infections as taught by Daley et al to administer to a patient with a bacterial infection (*S. aureus* and *P. aeruginosa* infections*)* because Blackburn et al discloses that a composition comprising lysostaphin and nisin provide broad range bactericidal activity against bacterial infections and the overall speed of bactericidal activity is enhanced when two bacteriocins are combined in one composition.

Applicant's Arguments

A) Applicant urges that the cited references, individually or combined do not suggest how to modify compositions and methods disclosed therein in order to produce the claimed invention. Applicant urges that the cited references do not provide a reasonable expectation of success for carrying out the claimed invention.

Applicant urges that even if combined Daley et al ('612) and Blackburn et al ('163) do not teach all elements of the claims, and do not enable one of ordinary skill in the art to practice the claimed invention. Applicant urges that ('612) describes compositions comprising lysostaphin in various surfactants to potentially produce a lysostaphin with enhanced biological activity and methods of using the composition to enhance lysostaphin bacterostatic and/or bactericidial efficacy against *S. aureus* Applicant urges that ('612) does not teach or suggest that a lantibiotic such as nisin and lysostaphin be combined in a single combination. Applicant urges that ('612) does not provide any support for a method of decolonizing bacteria at the site of infection. Applicant urges that ('163) fails to describe to one of ordinary skill in the art whether a topical formulation comprising a lantibiotic and lysostaphin would or would not be useful in a method of decolonizing bacterial populations at a bacterially infected site.

B) Applicant urges that as describe in the declaration submitted by Dr. James J Mond, one of ordinary skill in the art would not find examples or experimental data within ('612) that would allow one to practice the claimed invention. Applicant urges that Blackburn et al do not teach compositions used in the claimed method comprise 0.1 wt% lantibiotics and 0.1 wt% nisin.

C) Applicant urges that Daley et al ('612) and Blackburn et al ('163) do not provide reasonable expectation of success for carrying out the claimed invention. Applicant urges that the Examiner has mischaracterized the references. Applicant urges that the

argument that the cited references render the claimed invention prima facie obvious because it might appear obvious to try is legally supportable. Applicant urges that the Federal Circuit Court has expressly identified that this type of argument falls outside of the scope of the situation contemplated by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727(2007).

D) The Declaration submitted by Dr. James J. Mond discloses that Daley et al ('612) never discusses combining nisin and lysostaphin in one formulation. The Declaration urges that ('612) does not show any examples or give any information on how lysostaphin could be combined with nisin and does not mention any other lantibiotics other than nisin. The Declaration urges that ('612) has examples that look at lysostaphin activity *in vitro* in response to various surfactants assessed to their specific formulation and not relevant to our patent application. The Declaration discloses that ('612) is in contrast to the interaction of lysostaphin and lantibiotic topically applied to infected skin or wounds as described in their patent application.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed August 4, 2008 have been fully considered but they are not persuasive.

A) In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention

where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Daley et al ('612) teach a method of eliminating bacterial (*Staphylococcus)* infections (i.e. decolonizing bacterial populations) in bovine mammary glands comprising administering a composition comprising bacteriostatic peptide such as lysostaphin or nisin. Daley et al do not teach using other lantibiotics in the method of the invention. However, Blackburn et al teach compositions comprising lysostaphin and lantibiotics such as nisin and chelating agents and surfactants to treat or eliminate bacterial infections. One would be motivated to use a composition comprising lysostaphin, nisin, chelating agents and surfactants in a method to decolonize bacterial populations because Daley et al teach a composition comprising lysostaphin or nisin can eliminate bacterial (*Staphylococcus)* infections in bovine mammary glands and Blackburn et al teach that composition comprising lysostaphin, nisin, chelating agents and surfactants enhance broad range bactericides and are bactericidal in both gram-negative and gram-positive organisms (column 4).

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The

combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use lysostaphin and lantibiotics such as nisin to treat or eliminate bacterial infection. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results. Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness, absent evidence to the contrary.

B) To address Applicant's comments regarding the declaration submitted by Dr. James J. Mond, the declaration is insufficient to overcome the rejection under 35 U.S.C. 103(a) because as stated above, one would be motivated to use a composition comprising lysostaphin, nisin, chelating agents and surfactants in a method to decolonize bacterial populations because as stated above the prior art teaches that both lysostaphin and lantibiotics such as nisin can be used to treat or eliminate bacterial infection. Regarding the specific concentrations listed in the instant claims, MPEP 2144.05 states, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to

be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)."

C) To address Applicant's comment regarding "obvious to try", In response to applicant's argument that the examiner's conclusion of obviousness is based upon obvious to try, it should be noted that "obvious to try" is proper when there is a finding of a recognized problem or need in the art including a design need or market pressure to solve a problem, a finding that there has been a finite number of identified predictable potential solutions and a finding that one of ordinary skill in the art could have pursued the known potential options with a reasonable expectation of success. *See KSR International Co. v. Teleflex Inc.*, 220 U.S. -, 82 USPQ2d 1385 (2007). In the instant

case, the prior art has taught that a method of eliminating bacterial (*Staphylococcus)* infections in bovine mammary glands comprising administering a composition comprising bacteriostatic peptide such as lysostaphin or nisin (lantibiotic). The prior art has also taught that lysostaphin and other lantibiotics such as nisin reduce bacterial infections (e.g. *Staphylococcus aureus*). Therefore, the prior art teaches that a combination of lysostaphin and lantibiotics are effective at treating bacterial infection. Thus, in accordance with KSR International Co. v. Teleflex Inc., 220 U.S. -, 82 USPQ2d 1385 (2007) the standard of "obvious to try" is proper.

To address Applicant's arguments regarding reasonable expectation of success, the prior art Daley et al ('612) and Blackburn et al ('163) are have taught the success of using lysostaphin and lantibiotics such as nisin to treat or decolonize bacterial infections. Thus, the prior art has presented a reasonable expectation of success, that one of ordinary may conclude that the combination of lysostaphin and lantibiotics would be effective in decolonizing bacterial infection.

D) To address the declaration submitted by Dr. James J. Mond, the declaration is insufficient to overcome the rejection set forth under 35 U.S.C. 103(a).

To address the Declaration's comments regarding Daley et al ('612) never discussing a combination of nisin and lysostaphin, it should be noted that this rejection is a obviousness rejection and it is the combination of references that teach the claimed invention. Thus, ('612) need not teach the combination of nisin and lysostaphin

because this is a rejection made under 35 U.S.C. 103(a) and it is the combination of references that teach the claimed invention.

In view of all of the above this rejection is maintained.

5. The objection to the specification is maintained for the reasons set forth on pages 14-16, paragraph 5 of the previous Office Action.

The rejection is reiterated below:

Specification

The attempt to incorporate subject matter into this application by reference to WO 03/82124 (page 12 of specification) which is incorrect and should be WO 03/82124 is ineffective because MPEP 608 states:

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, Ex parte Schwarze, 151 USPQ 426 (Bd. Ape. 1966). An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application.

The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier. Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

Applicant's Arguments

Applicant urges that they have amended the specification to insert reference to U.S. Patent App. Pub. No. 20050118159 published on June 2, 2005.

Examiner's Arguments

It is the Examiner's position that the reference to U.S. Patent App. Pub. No. 20050118159 published on June 2, 2005 is improper. MPEP section 608 states:

37 CFR 1.57(f) addresses corrections of incorporation by reference by inserting the material previously incorporated by reference. A noncompliant incorporation by reference statement may be corrected by an amendment. 37 CFR 1.57(f). However, the amendment must not include new matter. Incorporating by reference material that was not incorporated by reference on filing of an application may introduce new matter. *An incorporation by reference of essential material to an unpublished U.S. patent application, a foreign application or patent, or to a publication is improper under 37 CFR 1.57(c)*. The improper incorporation by reference is not effective to incorporate the material unless corrected by the applicant (37 CFR 1.57(g)). Any underlying objection or rejection (e.g., under 35 U.S.C. 112) should be made by the examiner until applicant corrects the improper incorporation by reference by submitting an amendment to amend the specification or drawings to include the material incorporated by reference.

It should be noted that this application's *effective filing date* is December 10, 2002, since it claims priority to provisional application 60/432,182 filed December 10, 2002. Therefore, U.S. Patent App. Pub. No. 20050118159 published on June 2, 2005 did not exist on December 10, 2002. Thus, incorporation by reference is improper.

6. The rejection of claims 33-40, 42-46, 55-61 and 63-75 under 35 U.S.C. 103(a) is maintained for the reasons set forth on pages 16-19, paragraph 6 of the previous Office Action.

The rejection is reiterated below:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33-40, 42-46, 56-61 and 63-75 are rejected under 35 U.S.C. 103(a) as unpatentable over Blackburn et al (*U.S. Patent 5,762,948 published June 9, 1998)* in view of Gasson et al (*U.S. Patent 6,448,034 B1 published September 10, 2002).*

The claims are drawn to a method of decolonizing populations comprising topically applying to a patient in need thereof at a bacterially infected site a topical composition comprising lysostaphin and one or more lantibiotics.

Blackburn et al teach a method of disinfecting (decolonizing) bacterial populations comprising topically applying to a patient a topical composition comprising nisin and one or more lantibiotics such as lysostaphin (the Abstract, column 3 and columns 11 –12, Example 11). Blackburn et al teach that the lantibiotics are present at 25 ug/ml to 500 ug/ml in the compositions (column 15, claim 5). Therefore the prior art teaches a topical composition comprising a antibiotic from about 0.1 to about 10.0 wt %. Blackburn et al teach the compositions of the invention comprise chelating agents such as EDTA (column 3), a carrier for topical application such as a wipe or liquid (see the Abstract, column 3 and column 5), anti-infective active agents such as such as chlorhexidine (column 3), a skin absorption promoter such as monoglycerides and fatty acids (column 4) and surfactants such as polysorbate 20 (column 4). Blackburn et al teach that composition can comprise emulsifers (column 4). Blackburn et al teach a reduction in *Staphylococcus aureus* (columns 12-14).

Blackburn et al do not teach using nisin variants nisin variant H27K and nisin variant H31K.

Gasson et al teach nisin variants nisin variant H27K and nisin variant H31K.

Gasson et al teach that variant nisins which have improved properties compared with natural nisA nisin are preferred, for example those variant nisins which have more potent antimicrobial activity or that have greater resistance to hydrolysis or degradation when added to foodstuffs (column 6). Claim limitations such as "wherein the concentration of lysostaphin in said composition is lower than the minimum inhibitory concentration of lysostaphin when used independently", "wherein the concentration of lantibiotic in said composition is lower than the minimum inhibitory concentration of lantibiotic when used independently", wherein the concentration of lysostaphin and lantibiotic in said composition is lower than the minimum inhibitory concentration of lysostaphin and lantibiotic when used independently" would be necessarily taught by the prior art.

It would be *prima facie* obvious at the time the invention was made to modify the method of decolonizing bacterial infections as taught by Blackburn et al to administer to a patient with a bacterial infection (*S. aureus* and *P. aeruginosa* infections*)* a composition comprising lysostaphin and nisin variants H27K or H31K because Blackburn et al teach that compositions comprising lysostaphin and nisin can disinfect cow teat skin and reduce bacterial infection (Abstract and Example 11) and Gasson et al discloses that Gasson et al teach that variant nisins which have improved properties compared with natural nisA nisin are preferred, for example those variant nisins which have more potent antimicrobial activity. It would be expected absent evidence to the contrary that a composition comprising lysostaphin and nisin variants H27K or H31K would be effective in decolonizing a bacterial population, thereby by reducing bacterial infection.

Applicant's Arguments

Applicant urges that Blackburn ('948) fails to teach or suggest or enable all elements of the claimed invention. Applicant urges that ('948) fails to show experimental data using a composition that has both lysostaphin and a lantibiotic. Applicant urges that fails to teach the amount of nisin (lantibiotic) used by Blackburn is (25 ug/ml) and does not teach a lantibiotic that is 0.1 to 10.0 wt%. Applicant urges that Blackburn only teaches wipes formulated with nisin and not provide liquid formulations.

Applicant urges that ('034) (Gasson et al) do not supplement the deficiencies of ('948) and does not reference lysostaphin.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed August 4, 2008 have been fully considered but they are not persuasive.

It should be remembered that this a rejection made under 35 U.S.C. 103(a) and it is the combination of references that teach the claimed invention.

In this case, Blackburn et al ('948) teach a method of disinfecting (decolonizing) bacterial populations comprising topically applying to a patient a topical composition comprising nisin and one or more lantibiotics such as lysostaphin. Blackburn et al do not teach using nisin variants nisin variant H27K and nisin variant H31K. However, Gasson et al ('034) teach nisin variants, H27K and H31K. One would be motivated to use a composition comprising nisin variants (e.g. H27K and H31K) in a method of decolonizing bacterial populations because Gasson et al teach that nisin variants have improved properties compared with natural nisins and nisin variants have more potent antimicrobial activity.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use nisin variants because they have improved properties compared with natural nisins. Nisin variants have more potent antimicrobial activity. Thus, it would be obvious to apply a

known technique to a known product to be used in a known method that is ready for improvement to yield predictable results. Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness, absent evidence to the contrary.

In response to Applicant's comments regarding Blackburn et al ('948) teaching a composition that has both lysostaphin and a lantibiotic or teaching a composition wherein the amount of lantibiotic is 0.1 to 10.0% wt, it should be noted that Blackburn et al teach a composition comprising nisin, subtilin, epidermin, gallidermin, cinnamycin, duramycin, ancovenia or Pep5 (all of which are lantibiotics) and teach that lysostaphin may also be employed. Blackburn et al also teach these bactericidal agents (lysostaphin and lantibiotics) may be vary from 25 ug/ml to 500 ug/ml. See column 15, claim 5 of Blackburn et al. Regarding the specific concentrations listed in the instant claims, MPEP 2144.05 states, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at

1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)."

There is nothing on the record that teach or suggest that the combination of prior art references does not teach the claimed invention.

In view of all of the above this rejection is maintained.

7. The rejection of claim 41 under 35 U.S.C. 103(a) is maintained for the reasons set forth on pages 20-23, paragraph 7 of the previous Office Action.

The rejection is reiterated below:

Claim 41 is rejected under 35 U.S.C. 103(a) as unpatentable over Blackburn et al and Gasson et al as applied to claims 33-40, 42-46, 56-61 and 63-75 above and further in view of Krieger et al (*U.S. Patent No. 6,503,881 B1 published January 7, 2003).*

Claim 41 is drawn to the method of claim 33 wherein said topical composition further comprises at least one of bacitracin and necomycin".

The teachings of Blackburn et al and Gasson et al have been described previously.

Blackburn et al and Gasson et al do not teach the claim limitation "the method of claim 33 wherein said topical composition further comprises at least one of bacitracin and necomycin".

Kreiger et al teach bacitracin suppresses colonization of (*Staphylococcus aureus)* (column 37). Kreiger et al teach compositions and methods for treating infections, especially bacterial infections (see the Abstract).

It would be *prima facie* obvious at the time the invention was made to modify the method of decolonizing bacterial infections as taught by Blackburn et al to administer to a patient with a bacterial infection (*S. aureus* and *P. aeruginosa* infections*)* a composition comprising lysostaphin, nisin variants H27K or H31K and bacitracin because Blackburn et al teach that compositions comprising lysostaphin and nisin can disinfect cow teat skin and reduce bacterial infection, Gasson et al discloses that Gasson et al teach that variant nisins which have improved properties compared with natural nisA nisin are preferred, for example those variant nisins which have more potent antimicrobial activity and Krieger et al teach that bacitracin suppresses colonization. It would be expected absent evidence to the contrary that a composition comprising lysostaphin, nisin variants H27K or H31K and bacitracin would be effective in decolonizing a bacterial population, thereby by reducing bacterial infection.

Applicant's Arguments

Applicant urges that Blackburn ('948) fails to teach or suggest or enable all elements of the claimed invention. Applicant urges that ('948) fails to show experimental data using a composition that has both lysostaphin and a lantibiotic. Applicant urges that fails to teach the amount of nisin (lantibiotic) used by Blackburn is (25 ug/ml) and does not teach a lantibiotic that is 0.1 to 10.0 wt%. Applicant urges that Blackburn only teaches wipes formulated with nisin and not provide liquid formulations.

Applicant urges that ('881) (Krieger et al) do not supplement the deficiencies of ('948) and does not reference lysostaphin.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed August 4, 2008 have been fully considered but they are not persuasive.

It should be remembered that this a rejection made under 35 U.S.C. 103(a) and it is the combination of references that teach the claimed invention.

In this case, as described above, Blackburn et al ('948) teach compositions comprising lysostaphin and lantibiotics such as nisin and chelating agents and surfactants. Gasson et al teach that variant nisins which have improved properties compared with natural nisins and nisin variants have more potent antimicrobial activity. Blackburn et al nor Gasson et al teach the method of claim 33 wherein said topical composition further comprises at least one of bacitracin and necomycin". However, Krieger et al ('881) teach bacitracin suppresses colonization of (*Staphylococcus aureus)* (column 37). Kreiger et al teach compositions and methods for treating infections, especially bacterial infections. One would be motivated to add bacitracin in a composition comprising bactericidial compounds, lysostaphin and lantibiotics to be used in a method of decolonizing bacterial populations because Krieger et al teach that bacitracin suppresses colonization.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use bacitracin to suppress colonization. See Krieger et al. Thus, it would be obvious to apply

a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results. Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness, absent evidence to the contrary.

In response to Applicant's comments regarding Blackburn et al ('948) teaching a composition that has both lysostaphin and a lantibiotic or teaching a composition wherein the amount of lantibiotic is 0.1 to 10.0 wt, it should be noted that Blackburn et al teach a composition comprising nisin, subtilin, epidermin, gallidermin, cinnamycin, duramycin, ancovenia or Pep5 (all of which are lantibiotics) and teach that lysostaphin may also be employed. Blackburn et al also teach these bactericidal agents (lysostaphin and lantibiotics) may be at a concentration of 25 ug/ml to 500 ug/ml. See column 15, claim 5 of Blackburn et al. Regarding the specific concentrations listed in the instant claims, MPEP 2144.05 states, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also *Peterson*, 315 F.3d

at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)."

There is nothing on the record that teach or suggest that the combination of prior art references does not teach the claimed invention.

In view of all of the above this rejection is maintained.

8. The rejection of claim 62 under 35 U.S.C. 103(a) is maintained for the reasons set forth on pages 24-26, paragraph 10 of the previous Office Action.

The rejection is reiterated below:

Claim 62 is rejected under 35 U.S.C. 103(a) as unpatentable over Blackburn et al, *(U.S. Patent 5,762,948 published June 9, 1998)* Gasson et al (*U.S. Patent 6,448,034 B1 published September 10, 2002)* and Krieger et al (*U.S. Patent No. 6,503,881 B1 published January 7, 2003)* as applied to claims 33-46, 56-61 and 63-75 above and further in view of Anchisi et al *(I1 Farmaco (2001), p. 427-431*).

Claim 62 is drawn to the method of claim 43 wherein said emulsifier is an inverse emulsion of polyacrylamide in liquid paraffin.

The teachings of Blackburn et al, Gasson et al and Krieger et al have been described previously.

Blackburn et al, Gasson et al and Kreiger et al do not teach the claim limitation "wherein said emulsifier is an inverse emulsion of polyacrylamide in liquid paraffin".

Anchisi et al teach Sepigel 305 (an emulsifier which is an inverse emulsion of polyacrylamide in liquid paraffin) increases the stability of oil-in-water creams (see the Abstract). Anchisi et al teach that at a low concentration Sepigel 305 stabilizes emulsions in which the oil phase is essentially made up of a fluid oil (see page 430). Anchisi et al teach that Sepigel 305, not only makes the emulsification process easier but also prevents Phase Inversion Temperature (PIT) phenomena (page 431).

It would be *prima facie* obvious at the time the invention was made to modify the method of decolonizing bacterial infections as taught by Blackburn et al to administer to a patient with a bacterial infection (*S. aureus* and *P. aeruginosa* infections) a composition comprising lysostaphin, nisin variants H27K or H31K and bacitracin emulsified with Sepigel because Blackburn et al teach that compositions comprising lysostaphin and nisin can disinfect cow teat skin and reduce bacterial infection, Gasson et al discloses that Gasson et al teach that variant nisins have improved properties and have more potent antimicrobial activity, Krieger et al teach that bacitracin suppresses colonization and Anchisi et al teach Sepigel 305 (an emulsifier which is an inverse emulsion of polyacrylamide in liquid paraffin) increases the stability of oil-in-water creams. It would be expected absent evidence to the contrary that a composition comprising lysostaphin, nisin variants H27K or H31K and bacitracin emulsified in Sepigel would be a stable composition effective in decolonizing a bacterial population, thereby by reducing bacterial infection.

Applicant's Arguments

Applicant urges that the combination of references fail to teach or suggest the claimed invention. Applicant urges that Blackburn et al ('948) fails to show a composition that has both lysostaphin and a lantibiotic. Applicant urges that Gasson et al, Krieger et al and Anchisi et al do not supplement the deficiencies of ('948) and does not reference lysostaphin.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed August 4, 2008 have been fully considered but they are not persuasive.

It should be remembered that this a rejection made under 35 U.S.C. 103(a) and it is the combination of references that teach the claimed invention.

In this case, as described above, Blackburn et al ('948) teach compositions comprising lysostaphin and lantibiotics such as nisin and chelating agents and surfactants. Gasson et al teach that variant nisins which have improved properties compared with natural nisins and nisin variants have more potent antimicrobial activity. Blackburn et al nor Gasson et al teach the method of claim 33 wherein said topical composition further comprises at least one of bacitracin and necomycin". However, Krieger et al ('881) teach bacitracin suppresses colonization of (*Staphylococcus aureus)* (column 37). Kreiger et al teach compositions and methods for treating infections, especially bacterial infections. Anchisi et al teach Sepigel 305 (an emulsifier which is an inverse emulsion of polyacrylamide in liquid paraffin) increases the stability of oil-in-water creams. Anchisi et al teach that at a low concentration Sepigel 305 stabilizes emulsions in which the oil phase is essentially made up of a fluid oil. Anchisi et al teach that Sepigel 305, not only makes the emulsification process easier but also prevents Phase Inversion Temperature (PIT) phenomena.

One would be motivated to use an emulsifier which is an inverse emulsion of polyacrylamide in liquid paraffin in a method of decolonizing bacterial infections because Anchisi et al teach Sepigel 305 (an emulsifier which is an inverse emulsion of polyacrylamide in liquid paraffin) increases the stability of oil-in-water creams. It would be expected absent evidence to the contrary that a composition comprising lysostaphin, nisin variants H27K or H31K and bacitracin emulsified in Sepigel would be a stable

composition effective in decolonizing a bacterial population, thereby by reducing bacterial infection.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". It well known in the art to use bacitracin to suppress colonization. See Krieger et al. It is known in the art to use emulsifiers which are inverse emulsion of polyacrylamides in liquid paraffin. See Anchisi et al. Thus, it would be obvious to apply a known technique to a known product to be used in a known method that is ready for improvement to yield predictable results. Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness, absent convincing evidence to the contrary.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Status of Claims

10. No claims allowed.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Examiner, Art Unit 1645
November 20, 2008

/Robert B Mondesi/

Supervisory Patent Examiner, Art Unit 1645